

## BEST EVIDENCE TOPIC REPORTS

# Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary

Edited by B A Foëx

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Best Evidence Topic reports (BETs) summarise the evidence pertaining to particular clinical questions. They are not systematic reviews, but rather contain the best (highest level) evidence that can be practically obtained by busy practising clinicians. The search strategies used to find the best evidence are reported in detail in order to allow clinicians to update searches whenever necessary. Each BET is based on a clinical scenario and ends with a clinical bottom line which indicates, in the light of the evidence found, what the reporting clinician would do if faced with the same scenario again.

The BETs published below were first reported at the Critical Appraisal Journal Club at the Manchester Royal Infirmary<sup>1</sup> or placed on the BestBETs website. Each BET has been constructed in the four stages that have been described elsewhere.<sup>2</sup> The BETs shown here together with those published previously and those currently under construction can be seen at <http://www.bestbets.org>.<sup>3</sup> Three BETs are included in this issue of the journal.

- Detection of acute thoracic aortic dissection with D-dimer
- Epidural analgesia/anaesthesia versus systemic intravenous opioid analgesia in the management of blunt thoracic trauma
- Weather dependent nasal erythema in reindeer (*Rangifer tarandus*).

1 Carley SD, Mackway-Jones K, Jones A, *et al*. Moving towards evidence based emergency medicine: use of a structured critical appraisal journal club. *J Accid Emerg Med* 1998;**15**:220–2.

2 Mackway-Jones K, Carley SD, Morton RJ, *et al*. The best evidence topic report: A modified CAT for summarising the available evidence in emergency medicine. *J Accid Emerg Med* 1998;**15**:222–6.

3 Mackway-Jones K, Carley SD. [bestbets.org](http://www.bestbets.org): Odds on favourite for evidence in emergency medicine reaches the worldwide web. *J Accid Emerg Med* 2000;**17**:235–6.

thoracic aortic dissection. Seven papers were found addressing the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these papers are presented in table 1. The clinical bottom line is that a D-dimer value <500 ng/ml makes the diagnosis unlikely but there is still the possibility of a thrombosed false lumen.

### Three part question

In [emergency department patients with chest pain] can [D-Dimer] [detect acute thoracic aortic dissection]?

### Clinical scenario

A 71-year-old woman with a history of hypertension presents to the emergency department with a sudden onset of chest pain radiating to her back. Her ECG shows ischaemic changes and cardiac enzymes are pending. Chest x ray shows a normal appearing mediastinum but clinical suspicion for a thoracic aorta dissection remains. You wonder if a D-dimer assay has enough negative predictive value to exclude an acute thoracic aortic dissection (ATAD) to allow you to quickly anticoagulate this patient without any further imaging study.

### Search strategy

Medline 1950- August 2007 using the OVID interface, Cochrane Library (2007) [(exp Aneurysm, Dissecting/or Aneurysm/or aneurysm.mp.) OR (exp Aortic Aneurysm/or exp Aortic Aneurysm, Thoracic/or aortic dissection.mp.)] AND [(exp Fibrin Fibrinogen Degradation Products/or fibrinogen degradation products.mp.) OR (d-dimer.mp.)] LIMIT to human AND English.

### Search outcome

Ninety-five papers were found of which 88 were irrelevant or of insufficient quality, and seven were relevant and of sufficient quality for inclusion (table 1).

### Comments

D-dimers are specific cross-linked fibrin derivatives that are the product of fibrinolytic degradation. They are considered the best available marker of coagulation activity and are well studied as a marker in the diagnosis of pulmonary embolism (PE). D-dimer would theoretically be elevated in thoracic aorta dissection due to exposure of the false lumen. Chronic thoracic aorta dissection would theoretically not produce significant elevation in D-dimer secondary to endothelialisation of the false lumen. The clinical usefulness of a screening laboratory test for ATAD has several advantages. First, it would reduce the number of invasive diagnostic procedures as well as contrast induced nephropathy. Second, the rapid availability of the result would significantly reduce the time necessary to raise suspicion of ATAD. Third, a positive result could prevent patients from getting thrombolytic therapy when the

## Detection of acute thoracic aortic dissection with D-dimer

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### Abstract

A short cut review was carried out to establish whether a raised D-dimer could be used to identify patients with an acute

Table 1

Author, date, country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Perez <i>et al</i> , 2004, USA	156 patients with ATAD diagnosed in the ED. 7 had D-dimer drawn at presentation. 16 excluded for missing data	Retrospective chart review	Confirmed ATAD and D-dimer assay performed	All 7 patients with ATAD had elevated D-dimer (>500 ng/ml)	Retrospective study. Very few patients with ATAD had D-dimer drawn. Semi-quantitative D-dimer used, preventing determination of threshold that maximises sensitivity/specificity.
Eggebrecht <i>et al</i> , 2004, The Netherlands	64 consecutive chest pain patients had D-dimer drawn. 32 asymptomatic patients with chronic ATAD served as control group	Prospective cohort study	D-dimer in confirmed ATAD (>500 ng/ml)	All 16 patients with ATAD had higher D-dimer levels ( $2238 \pm 1765$ ) than those with chronic ATAD (314), AMI (171), or chest pain ( $p < 0.001$ ). Cut off value 500 ng/ml yielded sensitivity of 100% (95% CI 0.806 to 1.0) and specificity of 67% (95% CI 0.483 to 0.796).	No control group. Small number of patients. Coincidence that 64 consecutive patients yielded 16 patients with ATAD, 16 with PE, 16 with AMI, and 16 with non-cardiac chest pain?
Weber <i>et al</i> , 2003, Austria	10 ED patients with suspected ATAD. Retrospectively studied 14 patients with confirmed diagnosis of ATAD who also had D-dimer assay at presentation. 35 patients admitted with chest pain other than ATAD as a control group	Prospective cohort study	Confirmed ATAD with elevated quantitative D-dimer (>500 ng/ml)	D-dimer was elevated in all patients with ATAD (mean 9400 ng/ml, range: 630–54700 ng/ml). D-dimer also elevated in 11/35 (31%) control group patients	Study does not clearly identify how many of the 10 prospectively studied patients had ATAD. Abstract states that ATAD was suspected in the 10 prospectively studied patients but in the methods section it states that all 10 of these patients had ATAD. It is impossible to estimate sensitivity and specificity based on one group of patients with known ATAD and another group not suspected of ATAD. This study does not clearly account for all of the patients enrolled.
Akutsu <i>et al</i> , 2005, Japan	78 consecutive patients with suspected ATAD admitted to a coronary care unit who had a D-dimer assay at presentation. Later divided into ATAD (30) and non-ATAD (48)	Prospective cohort study	Confirmed ATAD with elevated quantitative D-dimer.	All 30 patients with ATAD had D-dimer >0.5 µg/ml	Small number of patients. Not an ED setting
Hazui <i>et al</i> , 2006, Japan	113 consecutive patients with ATAD who had a D-dimer assay at presentation	Retrospective cohort study	Cut off value 400 ng/ml. Compared sensitivity of D-dimer for detection of ATAD with and without thrombosed false lumen (TFL)	Sensitivity with TFL 86.4% (n=59), without TFL 98.1% (n=54). 9 ATAD patients (8%) with normal D-dimer	Small number of patients. Retrospective
Ohlmann <i>et al</i> , 2006, France	94 consecutive patients admitted with confirmed ATAD who had D-dimer assay at presentation. 94 matched controls presenting with clinical suspicion of dissection which was later ruled out	Retrospective case-control	Confirmed ATAD with elevated quantitative D-dimer	Sensitivity 99%. 93 of 94 patients had D-dimer >400 ng/ml. One false negative result: patient with TFL and D-dimer level of 300 ng/ml. 62 patients in control group (66%) had elevated D-dimer	Small number of patients. Retrospective
Hazui <i>et al</i> , 2005, Japan	29 consecutive ATAD patients, 49 consecutive AMI patients. Performed chest radiograph and D-dimer	Retrospective cohort study	Confirmed ATAD with elevated D-dimer	Sensitivity 93.1%. 2 patients with ATAD had D-dimer <800 ng/ml. Both had a thrombosed false lumen	Small number of patients. Retrospective. Patients with acute aortic dissection of the descending aorta only were excluded

AMI, acute myocardial infarction; ATAD, acute thoracic aorta dissection; ED, emergency department; TFL, thrombosed false lumen.

underlying aetiology of the patient's chest pain is ATAD. Finally, if the negative predictive value of D-dimer is high enough to exclude ATAD in patients with chest pain, anticoagulation could be initiated sooner in chest pain patients because treating physicians would not have to worry as much about ATAD masquerading as an acute coronary syndrome.

## ► CLINICAL BOTTOM LINE

Preliminary studies using D-dimer to exclude clinically suspected ATAD show promise. Clearly, the sensitivity of D-dimer for ATAD falls when a thrombosed false lumen is present. Large prospective validation studies need to be done before D-dimer can be used to dictate clinical decision making in emergency department patients suspected of having ATAD.

Perez A, Abbet P, Drescher MJ. D-dimers in the emergency department evaluation of aortic dissection. *Acad Emerg Med* 2004;**11**:397–400.

Eggebrecht H, Naber CK, Bruch C, *et al*. Value of plasma fibrin D-dimers for detection of acute aortic dissection. *J Am Coll Cardiol* 2004;**44**:804–9.

Weber T, Hogler S, Auer J, *et al*. D-dimer in acute aortic dissection. *Chest* 2003;**123**:1375–8.

Akutsu K, Sato N, Yamamoto T, *et al*. A rapid bedside D-dimer assay for screening of clinically suspected acute aortic dissection. *Circ J* 2005;**69**:397–403.

Hazui H, Nishimoto M, Hoshiga M, *et al*. Young adult patients with short dissection length and thrombosed false lumen without ulcer-like projections are liable to have false-negative results of d-dimer testing for acute aortic dissection based on a study of 113 cases. *Circ J* 2006;**70**:1598–601.

Ohlmann P, Faure A, Morel O, *et al*. Diagnostic and prognostic value of circulating D-dimers in patients with acute aortic dissection. *Crit Care Med* 2006;**34**:1358–64.

Hazui H, Fukumoto H, Negoro N, *et al*. Simple and useful tests for discriminating between acute aortic dissection of the ascending aorta and acute myocardial infarction in the emergency setting. *Circ J* 2005;**69**:677–82.

# Epidural analgesia/anaesthesia versus systemic intravenous opioid analgesia in the management of blunt thoracic trauma

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## Abstract

A short cut review was carried out to establish whether an epidural infusion provided any advantage over intravenous analgesia in the management of blunt thoracic trauma. Only four papers presented evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of this paper are presented in table 2. The clinical bottom line is that epidural analgesia may provide better pain relief, but may not alter clinical outcomes.

## Three part question

In a [patient with blunt thoracic injury] is an [epidural infusion rather than intravenous administration of opioids] [superior in relieving pain or reducing complications] from his chest wall trauma?

## Clinical scenario

A 65-year-old pedestrian involved in a road traffic accident has sustained four fractured ribs and has a small area of contused lung noted on the chest x ray. You wonder whether placement of an epidural catheter and infusion of opioid or local anaesthetic agents offers any benefit over intravenous opioid analgesics (by intermittent bolus or patient controlled analgesia) in relieving the patient's pain or reducing complications from his injury.

## Search strategy

Medline: [rib fracture.exp OR thoracic injuries.exp] AND [injections, epidural exp OR analgesic epidural exp]

Embase: [Thorax blunt trauma OR thorax injury OR rib fracture] AND [epidural anaesthesia OR thorax epidural]

Cochrane: Thoracic trauma

## Search outcome

Medline produced 56 papers, EMBASE 103, of which four were relevant and of sufficient quality (table 2).

## Comments

The limited quantity and quality of evidence illustrates the difficulties in studying this patient group and determining the most relevant outcomes. A significant number of patients will be excluded due to the presence of contraindications to epidural analgesia or to physician concerns that epidural analgesia may prevent continued assessment of the multiply injured patient. All four studies looked at slightly different patient groups, different treatment regimens and outcomes with consistently poor reporting of timing of placement of epidural catheters and administration of intravenous analgesics. Despite these limitations, the evidence hints that epidural analgesia/anaesthesia is superior to intravenous analgesia. However, it is very difficult to be confident that epidural analgesia/anaesthesia offers superior

pain relief and that this effect is translated into improved clinical outcomes with no significant side effects.

## ► CLINICAL BOTTOM LINE

On limited evidence from moderate quality studies, epidural analgesia/anaesthesia offers some benefits over intravenous analgesia but further studies are needed to strengthen this conclusion.

**Bulger EM**, Edwards T, Klotz P, *et al.* Epidural analgesia improves outcome after multiple rib fractures. *Surgery* 2004;136:426–30.

**Moon MR**, Luchette FA, Gibson SW, *et al.* Prospective randomised comparison of epidural versus parenteral opioid analgesia in thoracic trauma. *Ann Surg* 1999;229:684–91.

**Mackenzie RC**, Karaganes TG, Hoyt DB, *et al.* Prospective evaluation of epidural and intravenous administration of fentanyl for pain control and restoration of ventilatory function following multiple rib fractures. *J Trauma* 1991;31:443–9.

**Ullman DA**, Fortune JB, Greenhouse BB, *et al.* The treatment of patients with multiple rib fractures using continuous thoracic epidural narcotic infusion. *Reg Anesth* 1989;14:43–7.

# Weather dependent nasal erythema in reindeer (Rangifer tarandus)

Report by Stewart Teece and Bernard A Foëx, *Santa's little helpers*

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A short cut review was carried out to establish whether nasal erythema in a reindeer might be a useful navigational aid on Christmas Eve. From a search of nine papers, five presented evidence relevant to the question. The author, date and country of publication, "subjects" studied, study type, relevant outcomes, results and study weaknesses of these papers are presented in table 3. The clinical bottom line is that a reindeer with a red nose at rest at the North Pole would not inspire confidence.

## Three part question

[During inclement weather, especially low temperature and fog] is [nasal erythema in reindeer (mythical or otherwise)] a [good indicator of fitness for 24 h transglobal navigation and travel]?

## Clinical scenario

On Christmas Eve you intend to circumnavigate the globe stopping at every household containing a child in the space of one night using reindeer as your means of propulsion. However, it is a bit misty out and you fear this will make the task a little bit tricky: some sort of navigational aid would be helpful. You notice one of the reindeer has a very shiny red nose (you might even say it glows). All of the other reindeer are laughing and calling it names but you wonder whether this might be the answer to your navigational problems.

## Search strategy

Medline 1950–September 2007 using the OVID interface.(exp Reindeer/or rangifer tarandus.mp. OR reindeer.af.) AND [(exp nose/or exp rhinophyma/or exp rhinitis/OR (nose or rhinophyma or rhinitis).af. OR (snout or snorter or conk or neb or schnoz or hooter).af.)] no LIMITS.

Wikipedia: red-nosed reindeer.

Table 2

Author, date, country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Bulger <i>et al</i> , 2004, USA	46 patients >18 years of age with >3 rib fractures randomised to thoracic epidural (n=22) (bupivacaine, morphine or fentanyl) or systemic opioids (n=24) (morphine, hydromorphone and fentanyl) (patient controlled analgesia (PCA), or nurse administered if patient unable) (n=24). Excluded if had spinal injury, brain or spinal cord injury, altered mental state, unstable pelvic fracture, vascular instability. Also excluded if pain controlled with oral opioids or anti-inflammatory medication. Epidural consisted of bupivacaine, morphine and fentanyl.	Prospective non-blinded block randomised over 45 months	Primary end point was incidence of pneumonia as defined by Center for Disease Control. Duration of mechanical ventilation. Length of stay (LOS) in hospital and intensive care unit (ICU). Mortality. Complications	No significant differences in injury severity score (ISS) between groups but non-significant increase in numbers with flail chest, pulmonary contusions and chest tubes in epidural group. Significant difference in the development of pneumonia in epidural group vs systemic opioid group only if stratified for presence of additional pulmonary injury (OR 6.0, 95% CI 1 to 35; p=0.05) Significant increase in duration of ventilation for systemic opioid group IRR (incident rate ratio) 2.0 (95% CI 1.6 to 2.6 p<0.001) if groups stratified according to presence of pulmonary contusion. No difference in mortality, hospital length of stay (LOS) or ICU LOS or complications.	Small numbers. Non-blinded. No sample size calculation. 408 patients initially eligible but epidural was contraindicated in 282, and 80 refused consent. No details of timing of insertion of epidural or setting up of PCA or doses given. 3 patients in each group crossed over
Moon <i>et al</i> , 1999, USA	34 patients with blunt thoracic trauma (rib fractures, sternal fractures, flail chest, pulmonary contusion) randomly assigned either to thoracic epidural infusion of bupivacaine/morphine or morphine PCA device. Excluded if had contraindication to epidural catheter placement, Glasgow Coma Score <15, morbid obesity, pregnancy, labile blood pressure requiring vasopressors	Prospective non-blinded block randomised study over 19 months	10 point verbal rating pain scale performed at rest, on deep inspiration and movement. Pulmonary function tests including tidal volume (TV), forced expiratory volume (FEV) and maximal inspiratory force (MIF)	Significant reduction of pain scores on day 1 (5.8 vs 7.4) and day 3 (3.8 vs 6.2 (p<0.05) favouring the epidural group. Significant improvement in TV (590 ml vs 327 ml) and MIF (48 cmH <sub>2</sub> O vs 34 cmH <sub>2</sub> O favouring epidural group by day 3. No significant differences in FEV on any day between groups. Non-significant increase in LOS in epidural group	High patient withdrawal rate (10/34). Small numbers. No complications recorded. Results often shown graphically: values can only be estimated from graphs, or not put in at all. Study duration was only 3 days. No information on timing of epidurals or setting up of PCA devices.
Mackersie <i>et al</i> , 1991, USA	32 patients recruited with: -3 or more rib fractures; -2 or more rib fractures with pulmonary contusion; -flail chest/sternum; -two or more rib fractures with exploratory laparotomy. Randomly assigned to physician controlled intravenous fentanyl analgesia vs fentanyl epidural analgesia sited in lumbar area. Excluded if age <18, pregnancy, substance abuse, psychiatric disorder, spinal injury, chronic pain, particularly painful limb injury	Prospective block randomised study over 36 months	10 point VAS pain scores. Pulmonary function testing. LOS. Complications	Non-significant difference in mean time to initiation of analgesia for epidural and intravenous groups (7.9±7.0 h vs 6.9±6.7 h respectively). Significant increases for both epidural and intravenous groups in maximum inspiratory pressures (MIP) (17±20 and 5.3±19 cmH <sub>2</sub> O, respectively) and vital capacity (VC) (5.1±6.5 ml/kg and 2.8±4.5 ml/kg, respectively) compared to pre-analgesia level. Significant increase in PaCO <sub>2</sub> (5.6±4.2 torr) and decrease of PaO <sub>2</sub> (-19±14 torr) with intravenous analgesia. Significant decrease in pain scores in both epidural and intravenous groups at rest (-32±24 and -27±27, respectively) and on coughing/deep breathing (-42±25 and -25±26, respectively).	Small unblinded study. Analgesia controlled by physician, not patient. No statistical analysis of complications carried out. Groups matched for LOS, number of rib fractures and ISS
Ullman <i>et al</i> , 1989, USA	28 consecutive patients with multiple rib fractures randomly assigned to thoracic epidural opioid analgesia (n=15) within 72 h or intravenous morphine (n=13). Patients had to have significant pain—excluded if pain only on coughing or deep inspiration. Excluded if patient had head injury	Prospective, non-blinded randomised study over 2 years.	LOS in ICU and hospital LOS. Duration of ventilation. Need for tracheostomy	Epidural group had significant reduction in time on ICU (5.93±1.44 days vs 18.69±5.25 days, p<0.02). Epidural group had shorter hospital LOS (14.85±2.21 days vs 47.69±14.67 days, p<0.03). Epidural group had significantly less time ventilated (3.07±1.35 days vs 18.23±8.12 days, p<0.05). Epidural group had a lower incidence of tracheostomy (6.7±6.7% vs 38.5±14.0%, p<0.05)	Small study in select ICU population. Did indicate timing of placement of epidural catheter. Unblinded. Little information about other injuries though non-epidural group had a non-significantly higher ISS



Table 3

Author, date, country	Subjects	Study type	Outcomes	Key results	Study weaknesses
Blix and Johnsen, 1983, Norway	2 adult female reindeer in a climatic chamber exposed to ambient temperatures ranging from $-50^{\circ}$ to $+30^{\circ}\text{C}$ in winter and summer fur	Observational study	Exhaled air temperature, rectal temperature, minute ventilation, total respiratory heat loss (trhl).	Exhaled air temperature $20\text{--}22^{\circ}\text{C}$ below body temperature at lowest ambient temperatures, exponential increase in minute ventilation with ambient temperature in winter, trhl was lowest at lowest ambient temperatures	Neither of the reindeer could fly
Langman, 1985, The Netherlands	2 reindeer exposed to a variety of temperatures between $-5.5^{\circ}$ and $27.2^{\circ}\text{C}$	Observational study	Temperature of exhaled air at an ambient temp $<10^{\circ}\text{C}$ . Metabolic rates	Exhaled air $21^{\circ}\text{C}$ less than body temperature. At the lowest ambient temperature 75% of the heat added to the inspired air was recovered by the nasal counter-current heat exchange	No evidence reindeer expected to eat approx 1 billion carrots in next 24 h
Johnsen <i>et al</i> , 1985, Norway	Resin casts of reindeer nasal vascular architecture. 3 adult Norwegian reindeer trained to run on a treadmill in a climatic chamber	Observational studies	Anatomic and histological examination of the reindeer nose vasculature. Nasal mucosa temperature and expired air temperature	Reindeer have a parallel arrangement of communicating arterial and venous rete in the turbinates, which would act as a heat exchange mechanism. Optimisation of heat loss from mucosal surfaces during heat stress with cold venous effluent directed to the cavernous sinus for brain cooling	
Johnsen <i>et al</i> , 1987, Norway	Cineangiography of venous return in 3 adult reindeer subjected to either local or whole body thermal stimulation	Observational study	Blood flow	Superficial veins of the nose constricted during cold stress. During heat stress selective cooling of the brain by cold blood from the nasal mucosa	Probably the same 3 reindeer used in their previous study. The reindeer may have started to get fed up with all this
Johnsen and Folkow, 1988, Norway	7 winter-insulated adult female reindeer. In vitro studies of angular oculi and facial veins of adult reindeer	Observational studies	Blood pressure in the angular oculi and facial veins. Pharmacological stimulation of sections of facial vein and angular oculi veins	During severe heat stress dorsal nasal vein blood pressure increased in response to clamping the angular oculi vein. Facial veins lack $\alpha$ -adrenergic receptors, angular oculi veins lack $\beta$ -adrenergic receptors	

### Search outcome

Nine papers were found from Medline. Five helped answer the three part question; the others helped wrap presents. Wikipedia revealed Rudolph's story, but was a bit short on the science of his red nose.

### Comments

There appears to be no evidence for a specific disease state in reindeer, therefore nasal erythema may be due to increased blood flow to the nose. The differences in exhaled air temperatures at different ambient temperatures and the variations in total respiratory heat loss suggested the action of a nasal heat exchange mechanism. The papers by Johnsen *et al* (1985 and 1987) demonstrated the anatomical basis for the heat exchange mechanism. The study by Johnsen and Folkow (1988) suggested that the control of brain cooling is mediated by efferent sympathetic activity to the angular oculi and facial veins. During increasing heat stress cold venous return from the nose is switched from the facial veins to the angular oculi to effect preferential brain rather than body cooling. The distribution of adrenergic receptors means that for any change in sympathetic activity there are opposite effects on the two veins, allowing blood flow to be switched from one to the other.

It has been suggested, by Blix and Johnsen (1983), that in winter the nasal heat exchange mechanism restricts heat loss at rest, but, "in reindeer chased by wolves or tourists it serves as an important avenue of heat loss".

The evidence suggests that in winter resting reindeer will not have a red nose, but that when frantically circumnavigating the globe their noses will glow as they try to lose heat. A reindeer with a red nose at rest at the North Pole means either deranged temperature regulation, or the use of drugs. Neither of these conditions would inspire confidence for an arduous journey.

### ► CLINICAL BOTTOM LINE

A global positioning system is perhaps a more reliable navigational instrument than a reindeer with a brain at boiling point.

**Blix AS**, and Johnsen HK. Aspects of nasal heat exchange in resting reindeer. *J Physiol* 1983;**340**:445–54.

**Langman VA**. Nasal heat exchange in a northern ungulate, the reindeer (*Rangifer tarandus*). *Respir Physiol* 1985;**59**:279–87.

**Johnsen HK**, Blix AS, Jorgensen L, *et al*. Vascular basis for regulation of nasal heat exchange in reindeer. *Am J Physiol* 1985;**249**(5 Pt 2):R617–23.

**Johnsen HK**, Blix AS, Mercer JB, *et al*. Selective cooling of the brain in reindeer. *Am J Physiol* 1987;**253**(6 Pt 2):R848–53.

**Johnsen HK**, Folkow LP. Vascular control of brain cooling in reindeer. *Am J Physiol* 1988;**254**(5 Pt 2):R730–9.